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14. ABSTRACT

The current study sought to establish and test noninvasive neuroimaging methods to investigate the brain basis of cognitive decline in men on ADT. Healthy men showed better memory than men on ADT in a word learning task. Men with prostate cancer but who are not on ADT did not differ in memory from healthy older men. We found no group differences in several other cognitive tasks, including paragraph recall and the Trails task (a test of working memory). We compared brain activation during the word learning task in healthy men versus men on ADT. Although both groups activated the medial frontal gyrus when encoding words, activation was greater in men on ADT and men on ADT activate more regions, particularly in the prefrontal cortex, in order to encode information in memory. In conclusion, this pilot project suggests that neuroimaging methods can be useful in illuminating changes in brain activity that accompany behavioral loss of memory induced by ADT.

15. SUBJECT TERMS
prostate cancer; neuroimaging; neurocognition

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INTRODUCTION:

Androgen deprivation therapy (ADT) is an increasingly common treatment for advanced prostate cancer. Although some studies suggest that loss of testosterone may be a risk factor for cognitive decline, little is known about the neurocognitive changes associated with ADT. The current study sought to establish and test noninvasive neuroimaging methods to investigate the brain basis of cognitive decline in men on ADT. We sought to look at brain activity with function magnetic resonance imaging (fMRI) and integrity of brain white matter using diffusion tensor imaging (DTI). This work will give us much needed information in order to assess efficacy and adverse consequences of prostate cancer treatment on the brain. Such information is critical for treatment development and to allow patients, families and physicians to make informed choices among treatments in regards to optimal quality of life outcomes.

BODY:

Specific Aims

1) To develop diffusion tensor imaging and analysis methods to test the micromolecular structure and axon and myelin integrity in androgen deprived cancer patients.
2) To develop high resolution fMRI with a cognitive activation paradigm to investigate memory dysfunction in patients on androgen deprivation.
3) To test each method and obtain preliminary data on brain changes that occur with prostate cancer and androgen deprivation treatment as compared to healthy men.

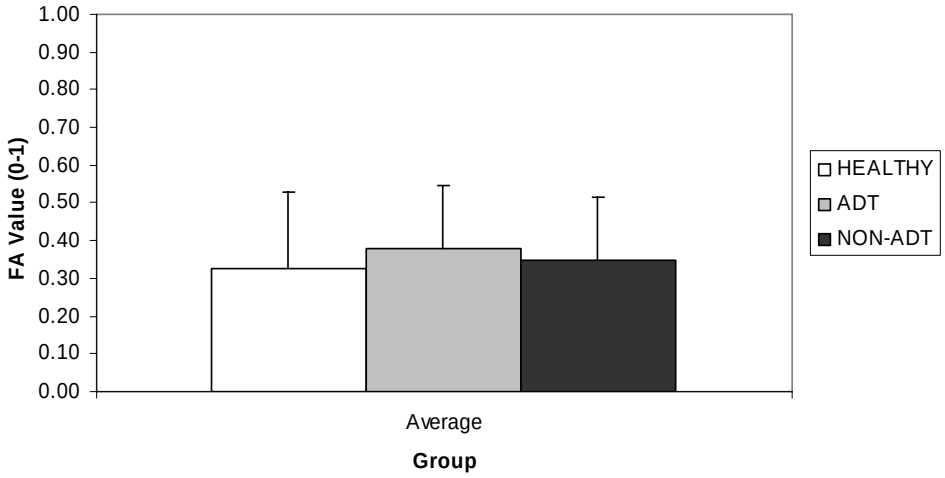
Findings and Results

Fourteen healthy older men have enrolled so far; 12 of these completed the behavioral, diffusion tensor imaging and fMRI data collection. Men completed behavioral measures of learning, memory, and mood as well as structural and functional MRI measures. We included also a measure of metamemory--how participants felt about their own memory. This measure taps people's contentment with their memory ability, beliefs about their memory ability, and use of strategies to help their memory. The healthy older men are compared to men with prostate cancer undergoing ADT (ADT), men with prostate cancer who are not on hormone treatment (Non-ADT). See table of subject characteristics.

Aim 1 & 3: The development of DTI.

We examined pilot DTI data collected with a Siemens 3T TIMS Trio MR system using a 12 channel head coil. We used the initial data to development an analysis plan. First we investigated differences in an obvious white matter pathway, the corpus callosum. FA in young and older pilot subjects (N=2 of each age) was compared. We used the software FSL http://www.fmrib.ox.ac.uk/fsl/]. Corpus callosum was outlined using visual anatomical landmarks in the midsagittal image. As expected from the literature, FA was lower in older men than younger men. The raw data files and our analysis was re-evaluated by our consultant Dr. David Salat to confirm appropriate use of the software and the same outcome. Subsequently, HEALTHY (N=9), ADT(N=5), and Non-ADT men (N=4) were assessed. Eight regions of interest were defined in prefrontal and parietal white matter based on (Salat et al., 2005). The following DTI sequence was used: 60, 2.5mm slices, TR 9000, TE 84ms, GRAPPA factor of 3. This sequence was repeated three times and data concatenated into a single dataset. We have completed an initial analysis thus far and do not find group differences in FA values (see Figure 1).

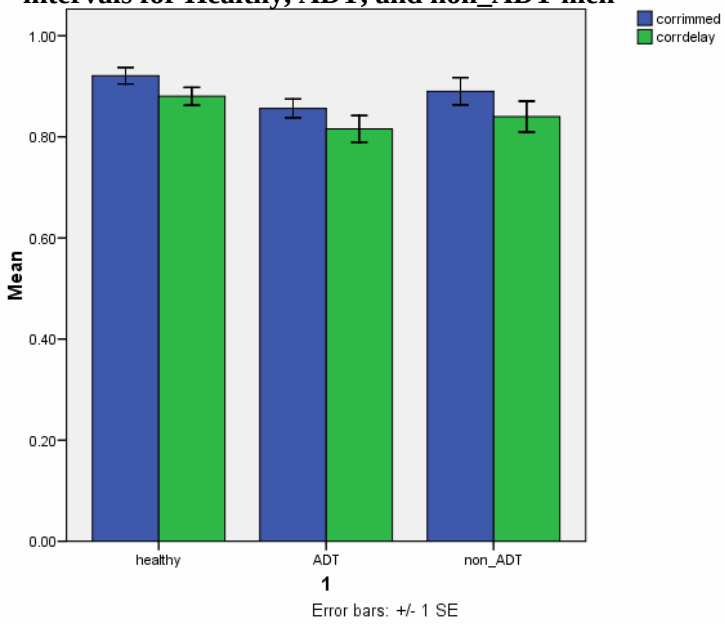
Figure 1. Average FA Intensity



This is an unexpected result. We have "back tested" the analysis with a sample of younger subjects and no do not find young/old differences with the ROI method as we found with callosum. Thus, we are currently reassessing each aspect of the imaging and analysis to see if the issue in obtaining the data, analysis, or if indeed there are no ADT effects on white matter diffusion. Our next step will include consultation with Dr. David Salat the consultant on this project.

Aim 2 & 3: We have developed a word memory task to be used in the MRI scanner and developed an analysis path using Brain Voyager software. We compare fMRI activity during the encoding of words. Previous studies have shown that brain activity at initial encoding predicts subsequent memory and that with aging there is amplification (compensatory) activity of prefrontal cortex. Healthy men show better memory than men on ADT for previously viewed words at both an immediate and a delayed recall (p = .06; see Figure 2). Men with prostate cancer but who are not on ADT do not differ in memory from healthy older men. We found no group differences in several other cognitive tasks, including paragraph recall and the Trails task (a test of working memory).

Figure 2. Word recognition at immediate and delay intervals for Healthy, ADT, and non_ADT men



We compared brain activation during this task in healthy men versus men on

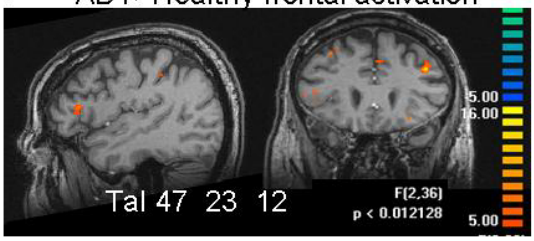
ADT. We found that although both groups activated the medial frontal gyrus when encoding words, activation was greater in men on ADT and men on ADT activate more regions, particularly in prefrontal cortex, in order to encode information in memory as compared to a matched group of healthy men (Table below).

ADT>Healthy			Talaraich coordinates				
Region	**BA**	**lat**	**x**	**y**	**z**	**# voxels**	**F-value**
Cingulate Gyrus	31	l	0	-36	26	618	6.0
Middle Frontal Gyrus	6	l	-28	1	43	443	7.6
Cingulate Gyrus	31	l	-14	-43	38	316	6.6
Middle Frontal Gyrus	8	l	-29	17	41	273	6.2
Precentral Gyrus	9	l	-43	23	35	265	7.2
Cingulate Gyrus	31	l	-16	-22	46	231	8.4
Precuneus	7	r	5	-45	45	1896	7.2
Paracentral Lobule	31	r	4	-21	45	437	6.7
Insula	13	r	35	-18	25	276	6.7
Inferior Frontal Gyrus	46	r	46	26	13	240	6.4
Inferior Parietal Lobule	40	r	39	-55	35	222	6.1

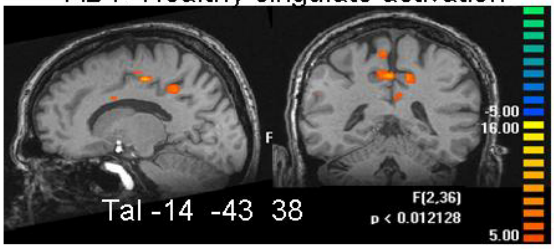
Table 1

The analysis utilizes random effects in the general linear model to show voxel clusters (>200 voxels/cluster, voxel size 1x1x1mm) that have significantly greater signal change in ADT than healthy men. The Table shows the regions with significantly more brain activity induced during word encoding in men on ADT as compared to healthy men (BA= Brodmann's area, lat=laterality). There is consistently greater activity in several prefrontal regions in men on ADT as compared to healthy men. In this contrast, there were no regions where healthy men had more activity than ADT men. Examples of the average activity differences (orange regions in prefrontal and cingulate), between ADT and healthy men is shown in the figure below. On going analyses and data collection are in process.

Fig. 3 ADT>Healthy frontal activation



ADT>Healthy cingulate activation



KEY RESEARCH ACCOMPLISHMENTS:

- We have designed and implemented neuroimaging indices of brain health for the study of longterm effects of ADT on the brain
- We have found that men on ADT show amplification of prefrontal activity as compared to healthy men. This type of activity increases in healthy aging and in with impending neurodegenerative disease suggesting that this profile may be a marker that ADT affects brain health.
- We have submitted a research proposal to follow up on this possibility.

REPORTABLE OUTCOMES:

Manuscripts

Krause, M. & Janowsky, J.S. (in progress). Metamemory and functional neuroimaging of episodic memory encoding in older men. *(indirectly related to ADT study)*

Abstracts

Krause, M., Roalf, D.R., & Janowsky, J.S. Metamemory and functional neuroimaging of episodic memory encoding in older men. Association for Psychological Science, 2007.

Janowsky, J.S., Neiss, M., Young, L., Krause, M. Testosterone modifies cognition and brain activity in aging. International Society for Behavioral Neuroscience 2007.

CONCLUSION:

In conclusion, this pilot project suggests that neuroimaging methods can be useful in illuminating changes in brain activity that accompany behavioral loss of memory induced by ADT. The study of additional subjects, problem solving the DTI analysis, and studying men with prostate cancer who are not on ADT will fully confirm the neurophysiological changes induced by loss of testosterone in elderly men. Future studies will examine whether longer term ADT confers increased risk and whether the physiological changes are precursors to progressive neurodegenerative disease.

REFERENCES:

Salat, D. H., Tuch, D. S., Greve, D. N., van der Kouwe, A. J., Hevelone, N. D., Zaleta, A. K. et al. (2005). Age-related alterations in white matter microstructure measured by diffusion tensor imaging. *Neurobiol.Aging, 26,* 1215-1227.

APPENDICES:

Abstract Submitted to Annual Meeting of the Association for Psychological Science, 2007.

Metamemory and functional neuroimaging of episodic memory encoding in older men.
Mark A. Krause, David R. Roalf, & Jeri S. Janowsky

Abstract
We examined the brain basis of episodic memory formation and its relationship to word recognition memory and self-reported metamemory in older men. Prefrontal cortical activity was related to recognition performance. Medial frontal activity was inversely related to self-reported memory ability, and positively related to the use of memory strategies.

Summary

Memory abilities, in particular episodic memory, decline as people age. Also, metacognitive awareness of one's own memory abilities (metamemory), changes with age. What is the brain basis of memory and metamemory change in older people? We used functional magnetic resonance imaging (fMRI) to examine relationships between prefrontal cortical activity during a semantic word encoding task, immediate and delayed (15-30 min) recognition for the words, and self-reported measures of metamemory in older adults.

A 3T MR scanner was used to measure blood oxygen level dependent (BOLD) brain activity in eleven healthy older men (Mean age 69.2 years) during a word encoding task. Subjects made a semantic discrimination (man-made versus natural) for words, and a perceptual discrimination about the orientation of a set of arrows. Stimuli were presented in random order for 750 ms followed by a 5250 ms blank screen. Participants responded using an MRI compatible key pad.

Subsequent recognition of words was tested under immediate and delayed (15-30 minute) retention intervals. Participants viewed the same words presented during encoding and an identical number of "distracter" words. They made one of three decisions (Yes: "know I've seen the word", Maybe: "may have seen the word", No: "know it is a new word") using the key pad. The Multifactorial Memory Questionnaire (MMQ; Troyer & Rich, 2002) was used to assess metamemory. The MMQ includes scales that measure contentment with one's memory, memory ability, and use of strategies to help remember. Participants rated questions on a 0-4 scale (occurs often vs. not at all; or strongly agree vs. strongly disagree) based on how they have felt the previous two weeks.

Word recognition was very good and declined between the immediate (93.2%) and delayed conditions (89.2), $t(10)=2.3$, $p < 0.05$. Ratings on the metamemory scales Contentment (3.1), Ability (2.9) and Strategy (1.7) were similar to previous reports (Troyer & Rich, 2002). Metamemory was not significantly related to immediate or delayed recognition performance.

Brain Voyager (vers. 1.7) was used to examine BOLD responses. A volume of interest analysis ($p < 0.01$, cluster size > 50) contrasting responses to words versus arrows revealed significant activation in the left medial, inferior and middle frontal gyri, right cingulate, and superior occipital gyrus. Time course data from these regions were extracted and peak activation of the averaged voxels within each cluster, controlling for baseline, was calculated separately for each subject. Peak activation of the left inferior frontal gyrus was inversely related to delayed word recognition ($r = -.64$, $p < 0.05$). A control region, the inferior parietal lobule, was positively related to delayed word recognition ($r = .78$, $p < 0.01$). Activation levels of the medial frontal gyrus were inversely related to self-ratings of memory ability ($r = -.65$, $p < 0.05$), and positively related to use of memory strategies ($r = .70$, $p < 0.05$).

Our initial analyses suggest that self-reported experiences of memory by older men (metamemory) do not predict memory performance. BOLD responses in specific regions of the frontal cortex are related to memory and metamemory.

Congressionally Directed Medical Research Programs
Prostate Cancer Research Program
2007 IMPaCT Meeting

The Brain Basis of Memory Loss with Androgen Deprivation Therapy: Methods Development and Preliminary Findings

Jeri S. Janowsky, Mark A. Krause and Tomasz M. Beer

Oregon Health & Science University

Androgen deprivation treatment (ADT) for prostate cancer is most common in the later decades of life when the risk for neurodegenerative disease is high. Testosterone plays both neuroprotective and neurotrophic roles in cortical regions of the brain important for cognition, and androgen receptors are found in regions critical for memory such as prefrontal cortex and hippocampus. Gonadectomy in rodent or non-human primate models results in an average loss of 40% of the synapses in the hippocampus, and testosterone replacement normalizes synaptic density. Androgen deprived rats and humans show increased levels of brain beta-amyloid, a significant risk factor for Alzheimer's disease, and low testosterone is a risk factor for Alzheimer's disease in men. Behavioral studies from our group recently showed that men with prostate cancer on ADT had impairments in verbal memory, but the brain basis of these cognitive changes is unknown. Modern neuroimaging methods permit the assessment of brain anatomy and function in humans and the ability to assess neurotoxicity in vivo. Thus, the goal of this study was to develop methods to investigate the brain basis of ADT effects on memory.

A 3-tesla MR system was used to examine brain function and structure. We used blood oxygenation level dependent changes as the functional (fMRI) measure of neural activity induced during learning and memory, and the anisotropy measure from diffusion tensor (DTI) magnetic resonance imaging (MRI) to examine brain white matter integrity. We compared brain activity during encoding of word lists and examined whether brain activity in the prefrontal cortex during learning predicted subsequent memory. We examined anisotropy in four white matter regions (prefrontal, callosum anterior and posterior, and parietal). These studies required that we test multiple methods of coregistration of diffusion and functional data with anatomy due to the variations in brain atrophy in this age range.

Memory performance and fMRI data from 12 healthy men, three men on ADT, and 2 men with prostate cancer but not on ADT (NoADT) matched for age other demographic variables have been compared using these methods. Men with ADT have worse memory than both healthy men and NoADT men. Brain activity in the prefrontal cortex is less in men on ADT than the other two groups during learning. Prefrontal activity predicts subsequent memory in all groups.

We conclude that both structural and functional MRI measures will be useful to identify the impact of long-term ADT on the brain and cognitive function. Initial results suggest that ADT results in a reduction in memory-induced brain activity that is accompanied by poorer memory performance. Our DTI measures will examine whether white matter loss accompanies these memory effects in men on ADT. Both fMRI and DTI can serve as biomarkers of brain health in cancer treatment studies.

Patients with prostate cancer and their physicians must weigh the potential benefits and risks of cancer treatments as well as when to initiate more aggressive therapies. The neuroimaging methods described here will provide an understanding of the effects of these therapies on the brain and may be particularly important for assessing the long term effects of cancer therapies on brain health.

The U.S. Army Medical Research and Materiel Command under W81XWH-06-1-0033 supported this work.